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MERCK
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Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane
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[Docket No. 01N-0322] Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews - Advance Notice of Proposed Rulemaking (ANPR)

Merck & Co., Inc, is a leading worldwide, human health product company that has produced many of the most important pharmaceutical products on the market, today. Merck's multidisciplinary Research and Development (R & D) is a highly risk-intensive process that depends upon a predictable regulatory environment. Merck supports regulatory oversight of product development that is based on sound scientific principles and good medical judgment.

In the course of bringing our product candidates through development testing and clinical studies, Merck medical professionals work regularly with thousands of clinical investigators, who will be affected by any new requirements for Institutional Review Boards (IRBs). Our discussions with these investigators and the process we use to secure the required decisions from IRBs, provide us with extensive experience from which to comment on this Advance Notice of Proposed Rulemaking (ANPR), entitled: *Institutional Review Boards: Requiring Sponsors and Investigators to Inform IRBs of Any Prior IRB Reviews,* hereafter referred to as the *ANPR on Prior IRB Reviews.*

General Comment & Questions

We commend FDA for taking the initiative to address any potential problem associated with investigators not informing an IRB about a prior unfavorable IRB review. However, the limited information of specific problems provided within this *ANPR on Prior IRB Review* raises the question as to whether or not a problem really exists.

- FDA states "that the Office of the Inspector General (OIG) never suggested that it was inappropriate to challenge a negative decision or to seek another IRB's review.[1]" If the OIG "...heard of a few situations...[2]" where this occurred, but did not recommend FDA action, why has FDA assumed the worst? Why has FDA concluded that investigators, unhappy with one IRB opinion, seek a 2nd IRB review and do not report the primary opinion to the 2nd IRB? Why does FDA presume that investigators participate in such practices at a rate that might warrant consideration of Rulemaking and pejoratively label this as "*IRB shopping?*"

01N-0322 C13

[1] 21 CFR Part 56: *Federal Register (FR)* Vol. 67, No. 44, Column 2, paragraph 3, lines 1-4
[2] 21 CFR Part 56: *Federal Register (FR)* Vol. 67, No. 44, Column 2, paragraph 2, lines 16

- If there is reason for FDA to hold the perception that the result of a primary IRB review would influence the outcome of a subsequent independent 2nd IRB decision, either negatively or positively, that information should be made public. Otherwise, the common understanding is that *independent* IRBs should function autonomously. Each has an obligation to seek external advice if the appropriate expertise is not represented among its members and each may vary in opinion about the importance and/or relevance of prior IRB decisions.

- Does FDA expect additional oversight of this process to prevent unscrupulous sponsors or investigators from seeking a 2nd IRB review after an unfavorable primary IRB opinion?

Merck recommends for FDA's consideration that there is insufficient information, either presented in this *ANPR on Prior IRB Review* or learned through our first-hand experience with the IRB system, that a problem of this sort exists. Indeed, there are a host of legitimate reasons, pertaining to IRB operational efficiencies, for investigators to selectively identify IRBs, some of which are described below.

Experience-based Observations

Legitimate Reasons to Selectively Seek IRB Reviews

As a sponsor of clinical investigations, Merck understands that there are significant legitimate reasons for an investigator to consider one IRB over another, *before* an IRB selection is made. Investigators usually select, and most sponsors recommend, IRBs with the *most timely* IRB decision-making or the *most cost-effective* IRB reviews, within certain geographic areas and within certain therapeutic disciplines. One might select a local IRB for review of a particular trial, but find that its schedule for decision-making may unnecessarily delay the onset of that trial, thereby necessitating a change of the IRB reviews site to another local institutional venue or to a central IRB.

It is also logical to assume that individual investigators pre-select IRB reviews to some extent, by evaluating the rapidity of prior opinions or by researching an IRB's members' expertise in a particular field of medicine. Indeed, sponsors like Merck typically will only reimburse an investigator for one IRB review of an original protocol and consent form. While this may provide incentive for careful pre-selections of IRBs by clinical investigators, it also discourages them from seeking 2nd opinions.

Incidence of Changing IRB Review Sites is Exceedingly Low

Since 1995, Merck has sponsored more than 2,100 clinical studies requiring that investigators secure IRB opinions from either local or institutional IRBs. In 2001 alone, Merck sponsored 1,300 clinical studies around the world, with associated IRB reviews at each study site. There has been only one occasion within the last 5 years, when Merck was consulted for our recommendation about contracting with a 2nd IRB. In that case, Merck was unwilling to accept the onerous reimbursement obligations that the IRB placed upon Merck in the event of Adverse Drug Reactions (ADRs) and it was recommended that a 2nd IRB be considered. Other than this experience, we are unaware of circumstances when a 2nd IRB opinion would be considered for any reason other than operational efficiency, such as timeliness of the review process and decision-making.

Our experience leads us to conclude that the incidence of investigators seeking a 2nd IRB review, because an investigator is "...unhappy with one IRB's reviews...,[3]" is exceedingly rare. In comparison to the numbers of IRB opinions that are rendered annually, this low rate is not significant enough to warrant unusual notice by IRBs, undue attention by the OIG or untoward speculation and/or unnecessary regulation by FDA. Given that operational efficiency and, perhaps, legal contractual issues may be the major reasons for considering a 2nd IRB, unnecessary FDA regulation might have the unintended effect of impeding clinical research by making it more difficult for investigators to select efficient and cost-effective IRBs.

Other Issues for Consideration

First, a problem that has not been adequately demonstrated or defined is difficult to solve. Therefore, recommending appropriate regulatory oversight and compliance actions or providing specific answers to FDA's questions posed in this *ANPR on Prior IRB Reviews* would be speculative at best.

Second, IRB operating procedures are being standardized and IRB auditing and accreditation procedures are being defined, all of which will address potential aberrations in the IRB process that might encourage what FDA defines as illegitimate *IRB shopping*. On the rare occasions when a 2nd opinion may be pursued, it should be left to individual IRBs to define requirements for the types of information and the timing of receipt of information that may be useful. Any new requirements should complement rather than confound the IRB's own operating procedures and be consistent with new IRB standards. Adding FDA regulation to the increasingly cumbersome processes currently being devised to quality assure the IRB system, would be premature. FDA involvement would likely add paperwork and cause additional, perhaps unnecessary, delays to efficiently conducting clinical trials.

Third, sponsors are not directly involved in the IRB decision-making process. For FDA to devise a more significant role for sponsors in that process introduces another level of *conflict of interest* that should not be acceptable either to investigators or to FDA. Alternatively, if FDA adds accountability of sponsors at the time when the clinical trials data are filed at FDA, that would amount to retrospective oversight that would probably not address problems identified here. Although there may be alternative times and places during the IRB review process when sponsors may be held accountable by FDA, defining them in the absence of explicit problems in these areas, will be very difficult.

Lastly, the operational and intellectual independence of IRBs may be compromised by opinions of prior IRBs. Individual IRBs, already overburdened with paperwork, might be bogged down by data on prior decisions, by evaluations of the qualifications of prior IRB decision-makers, or by a perceived obligation to devise additional levels of review or other mechanisms to impartially consider prior opinions.

Summary

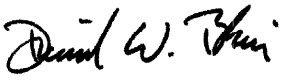
Merck concludes that there is insufficient reason for FDA to expect that patients' welfare is compromised by the practice of securing 2nd IRB opinions or that there is a high enough

[3] 21 CFR Part 56: *Federal Register (FR)* Vol. 67, No. 44, Column 2, paragraph 2, lines 18

incidence rate of irresponsible *IRB shopping* by investigators, to warrant FDA regulation, at this time. For a variety of legitimate reasons, investigators and sponsors may seek certain qualifications of IRBs before committing to an IRB's review. Since there are other institutional and operational processes that would be adversely impacted by FDA regulation, it would seem that FDA would be best advised to review this situation again, when the other checks and balances on IRB procedures are in place and in practice. Delaying FDA regulation at this time will also allow additional time for investigation of the issues raised here and collection of data on specific problems before FDA intervention in this complex process.

We welcome the opportunity to provide comments on this topic.

Sincerely,



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